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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/321,247	05/27/99	CHEN S	0443-2U2

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EXAMINER	
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ART UNIT	**PAPER NUMBER**
1636	11

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	09/321,247	CHEN ET AL.	
	Examiner	Art Unit	
	Bronwen M. Loeb	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 March 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-39* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-39* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *5* .
18) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other:

DETAILED ACTION

This action is in response to the Revocation of Power of Attorney received March 29, 2001.

Claims 1-39 are pending.

Specification

1. The disclosure is objected to because of the following informalities: the abbreviations RANTES and MIP are not defined.

Appropriate correction is required.

Claim Objections

2. Claims 13, 28, 32, 33 and 35 objected to because of the following informalities: claim 13 recites abbreviations, which have not been defined at their first use in the claims. In claim 28, in the phrase "said a receptor binding polypeptide", the "a" is redundant. In claim 32, to be consistent, "monocyte" and "macrophage" should be preceded with the article "a". Claim 33 recites abbreviations, which have not been defined at their first use in the claims. Claim 35 is objected to because it recites "a expression vector" which is grammatically incorrect; amending the "a" to an "an" would overcome this objection. Appropriate correction is required.

Double Patenting

3. A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or

discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

4. Claims 25-28 and 30-32 are provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 43, 47-50 and 52-54 of copending Application No. 09/322,275. This is a provisional double patenting rejection since the conflicting claims have not in fact been patented.

5. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Omum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

6. Claims 1, 2, 5-16, 18-22, 25-35 and 38 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 3, 6, 8-16, 18-20, 23, 26, 28-36, 38-42, 44-46 and 51 of copending Application No. 09/322,275. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the generic claims of

copending Application No. 09/322,275 render the species claims in the instant application obvious. The claims in copending Application No. 09/332,275, while broader than the instant claims, specifically recite the species claimed herein thus rendering them obvious.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 1-39 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The following factors have been considered in formulating this rejection (*In re Wands*, 858F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988): the breadth of the claims, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, the amount of direction of guidance presented, the presence or absence of working examples of the invention and the quantity of experimentation necessary.

The present claims are very broad. Claim 17 encompasses a method of inhibiting phenotypic expression of a chemokine receptor in a cell comprising blocking cell surface expression of said chemokine receptor. Claim 23 encompasses a method of inhibiting HIV infection of a cell by knocking out phenotypic expression of an HIV co-receptor. Inhibition of an infection reads on vaccination; thus claim 24 encompasses HIV vaccines. Claims 1 and 35 are drawn to an expression vector comprising a promoter, and a fusion of an intracellular retention signal sequence coding region to a chemokine encoding gene.

The nature of the invention is a method of treatment by inhibiting or knocking out phenotypic expression of chemokine receptors. The delivery of a nucleic acid in vivo or ex vivo for therapeutic purposes constitutes gene therapy. The only disclosed use for the vectors is gene therapy; they are examined in light of this intended use.

An analysis of the prior art as of the effective filing date of the present application shows the complete lack of documented success for any treatment based on gene therapy. In a review on the current status of gene therapy, Verma et al (Nature (1997) 389:239-242) state that despite hundreds of clinical trials underway, no successful outcome has been achieved. See Verma et al, p. 239, 1st paragraph. The continued, major obstacles to successful gene therapy for both viral vectors and non-viral methods are gene delivery and sustained expression of the gene. Viral vectors are additionally problematic because of host immune responses against them (p. 239, col. 3, 3rd paragraph). Regarding non-viral methods for gene delivery, Verma et al indicates that most approaches suffer from poor efficiency and transient expression of the gene (p.

239, col. 3, 2nd paragraph). While Verma et al indicate the promise of gene therapy, it is still a technique of the future and advancements in our understanding of the basics of gene delivery and expression must be made before gene therapy becomes a useful technique. See Verma et al, p. 242, col. 2-3.

The relative skill of those in the art of recombinant DNA techniques and gene therapy is high.

The area of the invention is unpredictable. As discussed above, the method of in vivo or ex vivo gene therapy is highly complex and unpredictable. Indeed, the recent tragic and unexpected death of a participant in a gene therapy clinical trial clearly illustrates the unpredictable nature of gene therapy. See Fox, ASM News, Feb. 2000, 66 (2): 1-3. The skilled artisan at the time the present invention was made recognized the difficulty of achieving sufficient heterologous gene expression to induce any therapeutic effect.

The present specification provides little or no guidance to support the claimed invention for gene therapy applications. While the specification discloses specific cell surface receptors to target in the case of HIV infection, it does not disclose specific chemokine receptors and their binding ligands to target in any other diseases. The specification discloses no specific therapeutic molecules and diseases to which the claimed vectors and methods can be applied. There is no direction provided as to how to overcome the obstacles to gene therapy recognized by leaders in the field, i.e. low efficiency of gene delivery and transient gene expression. The specification contemplates that because CCR5 expression is low, expression levels of the intrakines

to achieve therapeutic effect would not need to be high and could be achieved by currently known expression vectors (p. 8, lines 3-5). This statement however is purely speculative; there is no evidence provided to support it.

There are no working examples disclosed in which an HIV infection is treated by blocking chemokine receptor cell surface expression by any means, including expressing from an expression vector a gene encoding a fusion of the cognate chemokine to an intracellular retention signal sequence.

The quantity of experimentation necessary to carry out the claimed invention is high as the skilled artisan could not rely on the prior art or the present specification to teach how to use the claimed methods. In order to determine how to use the method to treat any condition mediated by chemokine receptor cell surface expression, one of skill in the art would have to determine what effect exogenous transgene expression would have in any cell type, whether the effect could be exploited for treatment of a disease, how to deliver the given nucleic acid to the appropriate target cells with specificity and efficiency, and how to get sufficient expression to induce at least some therapeutic effect. In order to determine how to use the method to treat HIV infection, one of skill in the art would have to determine what effect exogenous transgene expression would have in T4 cells and macrophages, whether the effect could be exploited for treatment of HIV, how to deliver the given nucleic acid to the appropriate target cells with specificity and efficiency, and how to get sufficient expression to induce at least some therapeutic effect. Since neither the prior art nor the specification provides the answers

to all of these questions, it would require a large quantity of trial and error experimentation by the skilled artisan to do so.

Based on the broad scope of the claims, the unpredictability in the area of the invention, the lack of sufficient guidance or working examples in the specification and the quantity of experimentation necessary, it would clearly require undue experimentation by one of skill in the art to determine how to use the claimed method of inhibiting phenotypic expression of a chemokine receptor in a cell in vivo, or the claimed method of inhibiting HIV infection of a cell in vivo.

With regard to claim 25, the specification does teach how the method is operative when the receptor binding polypeptide is not one which binds to the receptors recited in claim 24.

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claims 8-16, 19 and 23-39 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 8 recites the limitation "the C-C chemokine 5 receptor", "the C-C chemokine 3 receptor", "the C-C chemokine 1 receptor" and "the CXR4 receptor" in lines 2 and 3. There is insufficient antecedent basis for this limitation in the claim.

Claim 9 recites the limitation "the C-C chemokine 5 receptor" in line 2. There is insufficient antecedent basis for this limitation in the claim.

Claim 10 recites the limitation "the C-C chemokine 3 receptor" in line 2. There is insufficient antecedent basis for this limitation in the claim.

Claim 11 recites the limitation "the C-C chemokine 1 receptor" in line 2. There is insufficient antecedent basis for this limitation in the claim.

Claim 12 recites the limitation "the CXR4 receptor" in line 2. There is insufficient antecedent basis for this limitation in the claim.

Claim 13 is vague and indefinite in its recitation of "the encoded chemokine" in line 1. To which chemokine is this referring: the secreted one or the one fused to an intracellular retention signal sequence?

Claim 14 recites the limitation "the chemokine receptor" in lines 1-2. There is insufficient antecedent basis for this limitation in the claim.

Claim 15 is vague and indefinite as it is unclear to which chemokine the term "the encoded chemokine" refers.

Claim 16 recites the limitation "the expressed protein" in line 2. There is insufficient antecedent basis for this limitation in the claim.

Claim 19 is vague and indefinite because it recites the term "a chemokine analog". This is not a term of art and it is not defined in the specification.

Claim 23 is vague and indefinite as it lacks at least one active method step.

Claim 23 is also vague and indefinite because it lacks a step that clearly relates back to the preamble. Amending the claim to recite "wherein said phenotypic knock-out of an HIV co-receptor in said cell inhibits HIV infection of said cell" would overcome this rejection.

Claim 24 recites the limitation "the C-C chemokine 5 receptor", "the C-C chemokine 3 receptor", "the C-C chemokine 1 receptor" and "the CXR4 receptor" in lines 1 and 2. There is insufficient antecedent basis for this limitation in the claim.

Claim 28 recites the limitation "the receptor" in line 3. There is insufficient antecedent basis for this limitation in the claim.

Claim 28 is vague and indefinite because it recites the phrase "an analog of a CC or CXC chemokine". This is not a term of art and the specification does not define it.

Claim 35 is vague and indefinite. The "wherein" clause on p. 57, lines 1-3 renders the metes and bounds of the claim unclear as it is unclear whether the claim is drawn to an expression vector or to a method using the expression vector.

Claim 38 is vague and indefinite as it is unclear whether the claim is directed to an expression vector which happens to be in a pharmaceutically acceptable solution or if it is directed to a composition comprising an expression vector and a pharmaceutically acceptable solution.

Claim 39 is vague and indefinite as it lacks a step which clearly relates back to the preamble.

Claim Rejections - 35 USC § 102

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

12. Claims 17, 23, 24 and 32 are rejected under 35 U.S.C. 102(e) as being anticipated by Leavitt et al (USP 5,939,538). Leavitt et al teach a method of blocking HIV infection by blocking expression of HIV co-receptor RNA expression using ribozymes to cleave HIV co-receptor mRNA, or antisense molecules to bind the mRNA and inhibit translation. Inhibiting HIV co-receptor RNA expression will result in blocking cell surface expression of the co-receptor. Target cells for such treatment include T cells, macrophages and hematopoietic stem cells. See entire document, especially col. 5-16.

Conclusion

Claims 1-39 are rejected. Claims 1-16, 18-22, 25-31 and 33-39 are free of prior art.

Certain papers related to this application may be submitted to Art Unit 1636 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). The official fax telephone numbers for the Group are (703) 308-4242 and (703) 305-3014. NOTE: If Applicant does submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bronwen M. Loeb whose telephone number is (703) 605-1197. The examiner can normally be reached on Monday through Friday, from 10:00 AM to 6:30 PM. A phone message left at this number will be responded to as soon as possible (usually no later than the next business day after receipt by the examiner).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader, can be reached on (703) 308-0447.

Any inquiry of a general nature or relating to the status of this application should be directed to Dianiece Jacobs, Patent Analyst whose telephone number is (703) 305-3388.

Bronwen M. Loeb, Ph.D.
Patent Examiner
Art Unit 1636

July 16, 2001

ROBERT A. SCHWARTZMAN
PRIMARY EXAMINER